

NOTICE TO SHIPS' SURGEONS

SUGGESTIONS FOR THE PREVENTION, DIAGNOSIS AND TREATMENT OF MALARIA.

The recommendations relating to the prevention, diagnosis and treatment of malaria in the Ship Captain's Medical Guide have recently been revised, and have been issued as Amendment No. 3 to the present edition of that Book. A copy of that Amendment should be available on all foreign-going ships and Ships' Surgeons should make themselves familiar with its contents. The Amendment is, of course, primarily intended for the use of Masters of vessels that do not carry Surgeons, and the recommendations contained in it are confined necessarily to such measures of prevention and treatment as can be carried out by the layman. There are, however, other important measures which can be undertaken by Ships' Surgeons to reduce the morbidity and mortality due to malaria. The suggestions made in this Notice supplement the information given in Amendment No. 3 to the Ship Captain's Medical Guide. It is hoped that Ships' Surgeons who have had little or no opportunity for studying the disease will find this Notice useful.

Note.—This Notice supersedes Notice No. M. 195.

(1) GENERAL PRECAUTIONS

(i) Ships calling at malarious ports should lie as far off shore as possible, as mosquitoes may be carried long distances by wind from the shore.

(ii) Communication between the ship and the shore should be cut down to an absolute minimum, or even forbidden, between the hours of dusk and dawn. This applies especially to loading barges, fruit boats, etc., which are likely to carry infected mosquitoes from the shore to the ship.

(iii) If possible, portholes, doors, ventilators, etc., should be mosquito-proofed. This measure should be completed a day or so before arriving in a malarious area, and kept in operation for at least four days after leaving. Failing this, mosquito nets should be supplied to each member of the crew and to every passenger.

(iv) No one should be allowed ashore except for very urgent reasons, and no one should be allowed to remain ashore after dusk.

(v) No one should be allowed to sleep on deck, unless provided with a suitable mosquito net, which must be used in a proper fashion to prevent mosquito bites.

(vi) All lights not absolutely essential for the working of the ship, should be screened, as these are liable to attract mosquitoes from long distances.

(vii) After sunset all persons should wear sufficient clothing to protect the whole body from mosquito bites (long sleeves, long trousers, two pairs of socks, etc.). Fans are useful in helping to keep mosquitoes away,

but are *not* a certain protection. The exposed portions of the body (wrists, behind the ears, ankles, back of neck, etc.) should be smeared with culicifuges after dusk. The best is dimethyl phthalate (DMP).

It must be remembered, however, that the effects of these substances only last for about three hours or so, and that the application must then be renewed.

(viii) Cabins, bathrooms, etc., should be sprayed before bedtime and in the early morning. Special attention should be given to all dark corners, the inside of wardrobes, spaces under bunks, behind baths, etc. Insecticides containing DDT or "Gammexane" and pyrethrum are especially useful. Sticks of incense burning in cabins will also tend to keep mosquitoes away.

(ix) Curtains and other materials hanging in the cabins should be well shaken and any mosquitoes destroyed before turning in.

(x) Bathing should be carried out during the hours of daylight and not after dark.

(xi) All persons feeling "off colour" should report to the Medical Officer at once, as this may be a premonitory symptom of a malarial attack, and early treatment is absolutely essential.

(2) MEDICAL PRECAUTIONS

When a vessel is proceeding to a malarious area it will be necessary to resort to the use of drugs for suppressive treatment.

It must always be remembered that such suppressive treatment does not prevent a person contracting malarial infection. While the drug is being taken regularly in proper dosage, clinical attacks will be held in abeyance, the severity of attacks will be reduced, and the mortality rate be very low.

Persons who have become infected but have not developed symptoms during the time while the "suppressive" drug was being taken, may develop malaria some days, weeks or months after the drug is stopped. It is necessary, therefore, to watch for such attacks. All persons should be warned that they have been exposed to the chance of infection, and that, if they fall ill at a later date, they should inform their medical attendant that the ailment from which they are now suffering may be of malarious origin.

The taking of prophylactic drugs should not be left to the individual, but should be supervised officially. There should be an official muster for this purpose (preferably after some meal), and a responsible officer should be entrusted with the duty of seeing that *all* persons on board receive and swallow the prescribed dose of drug. For this purpose a nominal roll should be kept to ensure that no one escapes.

The drugs of practical value for this purpose are "Paludrine," mepracrine and quinine.

(i) "Paludrine" Suppressive Treatment. "Paludrine" is the most satisfactory and the most effective drug known for the suppression and prevention of malaria. One tablet (0.1 gramme) should be given to adults



(or children over the age of 14 years)* under supervision every day, commencing at least 24 hours before reaching the malarious port and continuing every day while in port and for 30 days after leaving port. Where several malarious ports are visited one tablet should be taken every day during the voyage, commencing 24 hours before arrival at the first malarious port.

When taken for the suppression or prevention of malaria, "Paludrine" possesses certain advantages over mepacrine in that (1) it does not discolour the skin (2) it is less likely to cause unpleasant toxic symptoms (3) it need not be given until 24 hours before reaching the first malarious port (4) it is a true causal prophylactic in malignant tertian infections destroying the pre-erythrocytic parasites.

(ii) **Mepacrine Suppressive Treatment.**—The dosage for adults is one tablet (0.1 gramme) daily. It should always be given after food and followed by a copious draught of water. The morning or forenoon is a better time to take it than later in the day. Although *extremely* rare, the unpleasant by-effects mentioned in Appendix II should be watched for, in persons who may have an idiosyncrasy. Mepacrine may cause a yellow discoloration of the skin. This is *not* a toxic manifestation and should not be mistaken for jaundice. It is due to the dye element in the drug.

Suppressive treatment should be started 10 days before the malarious port is reached and should be continued for 30 days after the risk of infection or re-infection has passed. The satisfactory results produced by this drug, are dependent upon the strict regularity with which it is taken daily.

The dosage for children should be similar to that suggested for "Paludrine" (see footnote*).

(iii) **Quinine Suppressive Treatment.**—The usual dosage is 5 grains daily, but this may need to be increased to 10 grains in the presence of intense malaria. Solutions should be given wherever possible. If tablets must be used, they should be those of some very soluble quinine salt, such as the dihydrochloride or bisulphate. These should *never* be sugar coated. Their solubility should be tested periodically by placing one in a glass of water. If it does not disintegrate and dissolve in a few minutes, the tablets should be well crushed or put into solution before use.† Tablets are better given after meals or followed by copious draughts of water.

The dosage for children should be similar to that suggested for "Paludrine" (see footnote*).

The treatment should start on the day before arrival in port and continue for at least one month after leaving. As a suppressive drug quinine is inferior to either "Paludrine" or mepacrine.

* Children under 14 years of age must be given a reduced dose as follows :—

0-7	Quarter of a tablet
8-14 years	Half of a tablet
14 years and over	Adult dosage

† In young children, who may not swallow tablets well, the crushed tablets may be given with jam, sweetened milk, etc.

(3) CLINICAL MANIFESTATIONS OF MALARIA

Malaria is a disease caused by plasmodial parasites which attack and destroy the red cells of the blood. This gives rise to febrile manifestations and anaemia. Debility, jaundice and splenomegaly may follow, more especially in chronic and untreated cases.

The malarial fevers can be caused by at least four different species of malarial parasite :—(a) *Plasmodium vivax*, the parasite of benign or simple tertian malaria, which has a cycle of 48 hours, and so gives rise to fever every other day in single infections ; (b) *P. malariae*, the parasite of quartan malaria, which has a cycle of 72 hours and so gives rise to fever after afebrile intervals of two days, in single infections ; and (c) *P. falciparum*, the parasite of malignant tertian, subtertian, tropical or aestivo-autumnal malaria, which has a cycle like *P. vivax* ; and (d) *P. ovale*, the parasite of a very mild tertian infection, confined almost entirely to equatorial Africa.

The pathological effects of the first two parasites are seldom dangerous to life in adults, but may be so in infants and children, especially if these be debilitated or under-nourished. Infections of *P. falciparum* are, however, liable to cause pernicious manifestations, which often end fatally, unless treatment be started *very* early in the attack (*vide infra*).

The classical attack of malaria is characterised clinically by the occurrence of acute febrile paroxysms at definite intervals (24, 48 or 72 hours) (*vide charts 1-6*). The fever also shows a great tendency to recur, following upon varying periods of apyrexia after the primary febrile attack has been cured, either by therapeutic or natural means.

A. Typical Attacks

After vague premonitory symptoms lasting a few days, the typical paroxysm of fever develops, showing the three classical stages—(i) a cold or shivering stage (“ rigor ”) ; (ii) a hot or fever stage ; and (iii) a sweating stage, followed by an apyrexial interval.

(a) *Premonitory Stage*. For several days before a frank attack occurs, the patient may complain of headache, lassitude, pains in the bones, or limbs, loss of appetite, etc. Occasionally vomiting occurs. At this stage fever can often be detected if the temperature be taken four-hourly, but parasites may be difficult to find in the peripheral blood.

(b) *Paroxysm*. (i) *Cold Stage*. Chilliness, shivering of body and chattering teeth ; cold blue skin and nails ; pains in head and body ; frequently nausea and vomiting,* temperature rising rapidly. (ii) *Hot Stage*. Cold feeling abates ; skin hot and dry ; face flushed ; great thirst ; pains increased ; drowsiness, coma or delirium in severe cases ; perhaps convulsions in children. Temperature high, perhaps 105°F. or more ; pulse, hard, quick

* In severe cases this has been mistaken for food poisoning, and may indicate the start of the algid of the gastro-intestinal types of malignant tertian malaria (*vide infra*).

TYPES ON TEMPERATURE IN MALARIAL FEVERS.

CHART 1.

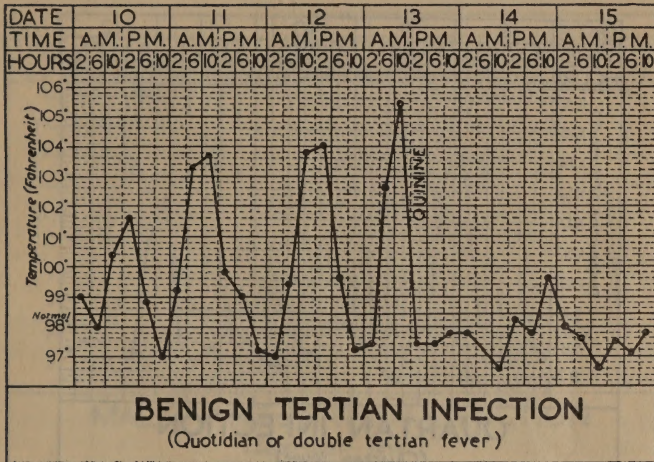
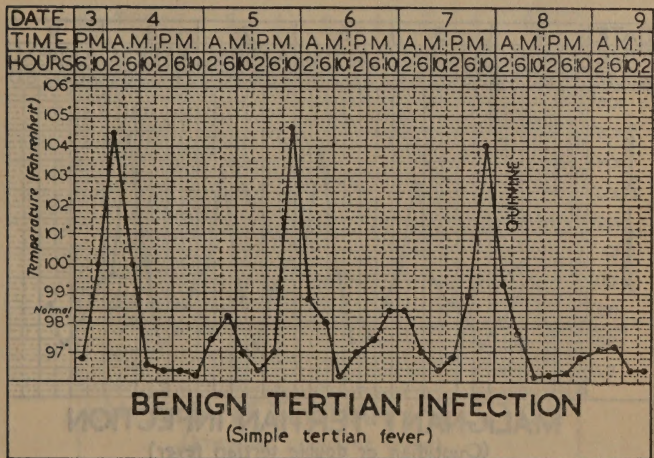


CHART 2.



TYPES ON TEMPERATURE IN MALARIAL FEVERS.

CHART 3.

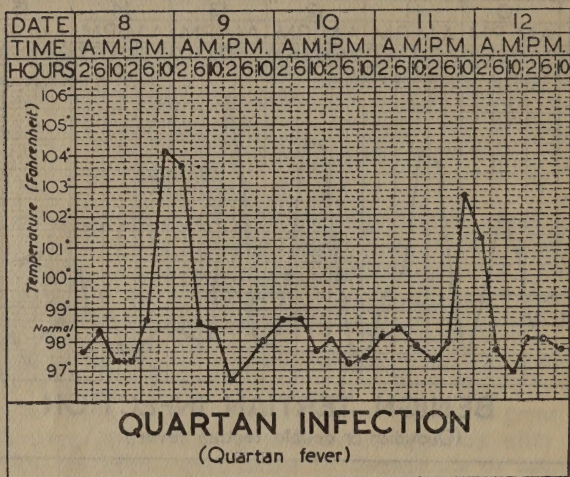
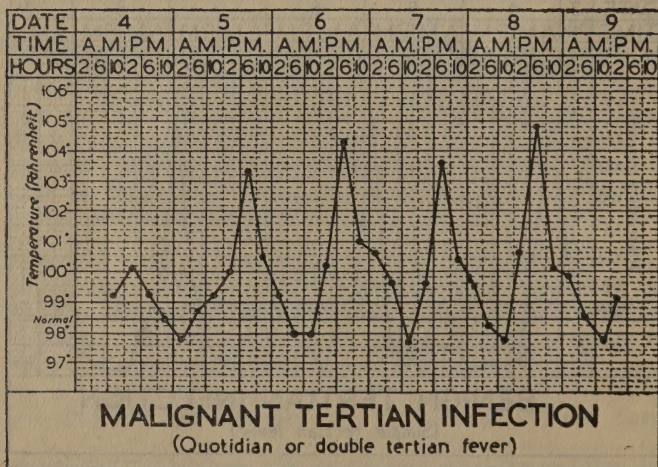


CHART 4.



TYPES ON TEMPERATURE IN MALARIAL FEVERS.

CHART 5.

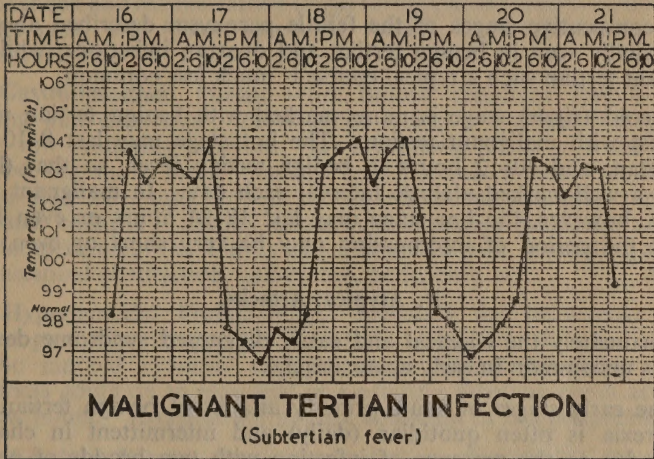
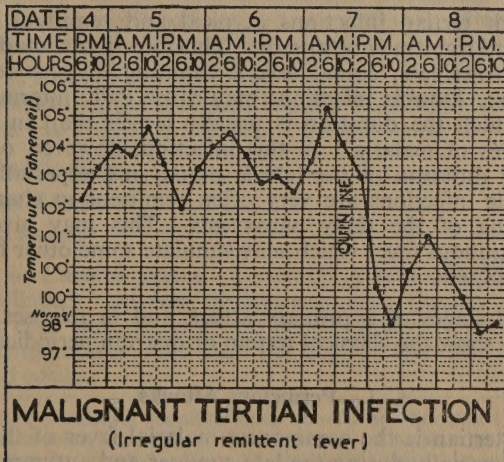


CHART 6.



and full. (iii) *Sweating Stage*. Profuse sweating ; relief of symptoms ; temperature and pulse rate fall rapidly and sleep may follow.

- (c) **Apyrexial Interval**. The whole paroxysm usually lasts about 8–10 hours, or perhaps 24 hours in malignant tertian infections. In the interval the patient feels washed-out and languid, but otherwise well. Temperature usually subnormal. The attack may be repeated in 24, 48 or 72 hours.

The consecutive stages of the febrile paroxysm described above are more usually seen in benign tertian and quartan infections, while with malignant tertian such a typical course is much less common.

The cold (rigor) stage is more marked with benign tertian malaria and least with malignant tertian. The hot stage may last 8–10 hours in quartan, and 10–12 hours in benign tertian fever, so that there is usually a well-marked afebrile interval each day. In malignant tertian malaria, however, the hot stage may last 18–24 hours or even longer, so that the period of intermission may be very short or even absent entirely.

B. Atypical Attacks.

Unfortunately the classical and easily diagnosed syndrome described above is uncommon in early acute attacks.

In the early stages of acute primary attacks of benign tertian fever, the pyrexia is often quotidian (daily) and intermittent in character. This is due to the presence of infection with two broods of parasites segmenting on alternate days. In quartan malaria, two such broods may cause intermittent fever on two days followed by an apyrexial interval of one day, then fever on two more days and so on, while three broods of parasites in such infections may cause daily intermittent fever.

In malignant tertian infections atypical and remittent temperatures are the rule, and rigor may be absent. This infection should be suspected if delirium, drowsiness, coma, severe vomiting, hyperpyrexia or early jaundice occur. Double infections may cause daily intermittent attacks of fever of which the duration is usually longer than in either of the other two types of malaria. In this infection, however, on account of the prolonged duration of the febrile paroxysms, especially in primary attacks, double infections are very often remittent in character due to the overlapping of the daily paroxysms. This may give rise to an irregular, continuous fever which may simulate some other febrile disease such as typhoid, etc.

In the later stages of a primary attack and in relapses, the fever is more likely to show the classical tertian or quartan periodicities.

C. Pernicious Attacks.

Malignant tertian is the commonest malarial fever of the tropics and sub-tropics, especially during the late summer and autumn. A look-out must always be kept for the severe manifestations which may accompany

this form of fever. Their onset may be very sudden, leading to pernicious complications and death in a few hours. The onset may be preceded by mild premonitory symptoms, such as general malaise, tiredness, headaches, etc., with few or no detectable parasites in the peripheral blood. The patient may continue at his work in spite of these, and medical aid may only be called in when it is too late.* Such dangerous manifestations may be shown as continuous high temperature, hyperpyrexia, signs of involvement of the central nervous system (cerebral forms), signs of shock and cardiac failure (algid forms), severe vomiting, diarrhoea, haematemesis, etc. (gastro-intestinal forms), haemoglobinuria (black-water fever), etc.

(i) **Gastro-intestinal Forms.**—(a) Bilious remittent fever—bilious vomiting and diarrhoea; pronounced icterus; typhoid-like remittent fever; low muttering delirium. (b) Dysenteric forms with the passage of blood but more rarely mucus. (c) Choleraic forms with vomiting profuse diarrhoea, may be with blood and mucus, cramps, suppressed urine and collapse; usually numerous detectable parasites, and high rectal temperature. (d) Forms with abdominal pain, simulating appendicitis, intestinal obstruction, gall-stones, peritonitis, etc.

(ii) **Hyperpyrexial Forms.**—Often mistaken for heat-stroke; temperature gradually rising to 105°F., 107°F. or higher; skin, hot and dry; may be marked cyanosis or dyspnoea; violent headache, perhaps drowsiness going on to maniacal or muttering delirium, coma and death in a few hours. Parasites are usually abundant in the peripheral blood.

(iii) **Cerebral Forms.**—Premonitory signs:—drowsiness, intense and generalised headache; stiff-neck; nervous twitching; restlessness; peculiarity of behaviour; slight delirium, etc.

(a) **Comatose** forms may come on suddenly, but often show premonitory symptoms; apathy and drowsiness, increasing to stupor and coma; face suffused, pupils contracted, altered knee-jerks, temperature usually high, but not necessarily so. Parasites may be very scanty in peripheral blood.

(b) **Epileptiform**—great and acute psychological disturbances; excitability; tendency to violence, delirium, convulsions.

(c) **Encephalitic forms.**

(d) **Meningeal forms.**

(e) **Paretic forms.**

(iv) **Algid or Cardiac Forms.**—Resembling acute shock—rapid loss of strength; collapse; extreme cardiac weakness, thready pulse; intense perspiration, cold skin, Hippocratic facies, shallow breathing. Axillary and rectal temperatures often high but skin temperature low. Parasites usually found easily.

* The onset of pernicious manifestations should be anticipated and appropriate measures taken *at once*, especially if the conditions of parasite prevalence described in the next section be detected. These attacks should always be considered as acute medical emergencies. They are particularly common in the late summer and autumn, and in children.

(v) **Haemoglobinuria.**—Blackwater fever is not a typical manifestation of an acute primary attack, but may occur in chronic infections. This serious syndrome is accompanied by fever, remittent or intermittent; rigors are common; jaundice may appear early and become intense; vomiting is usual. The urine at first may be pink or bright red, but soon becomes dark red, brown or even black, due to the presence of oxyhaemoglobin, methaemoglobin and urobilin (haemoglobinuria not haematuria); abundant albumen and casts. The patient is anxious and restless; the pulse weak, rapid and soft. Cardiac failure is the commonest cause of death.

D. Relapses.

Relapses are a characteristic of malarial fevers, more especially in untreated or imperfectly treated patients. Malignant tertian infections very seldom relapse with clinical symptoms after one year nor benign tertian after 3 years, but quartan infections have been known to last 7 years or more. Relapses of *ovale* infections are almost unknown.

Relapses occur most commonly as the result of:—

- (a) Stoppage of suppressive treatment;
- (b) Excessive cold, fatigue, exposure, etc.;
- (c) Intercurrent infections;
- (d) Anaesthesia, injury (either surgical or accidental), haemorrhage;
- (e) Protein shock due to injections of serum or vaccines, blood transfusions, etc.

The manifestations of such relapses are more commonly of the classical type and pernicious attacks are less frequent, but blackwater fever may occur.

E. Malaria in Children.

The effects of this disease fall more heavily on the child population than on the adult one. In highly malarious areas the infantile mortality may be twice as high as that seen in non-malarious localities.

Children are specially prone to pernicious manifestations, and, while most of the mortality is usually due to malignant tertian infections, benign tertian and quartan ones can also prove fatal, especially in debilitated and under-nourished children. The weakening effects of chronic infections make children liable to contract intercurrent infections which may be the ultimate cause of death.

Acute attacks are rarely typical, and clinical diagnosis is difficult. Severe headache may be complained of; drowsiness and yawning may be noticed; intense thirst is often present; fever occurring at night may be overlooked, and convulsions, which are not rare, may be the first sign noted by the parents, apart from general lassitude. Vomiting is common and diarrhoea may occur. A typical rigor is rare; fever is usually high and less regular than in adults. The spleen is detectable more often. Chronic infections with progressive anaemia, debility and splenic enlargement are frequently overlooked until the child becomes seriously ill.

Malaria in a child must always be suspected in any illness, especially a febrile one, occurring in or after a stay in a malarious area, and should be regarded seriously.

F. Malaria in Pregnancy.

Malarial infections during pregnancy are a common cause of abortion and premature labour. This is especially the case if early and adequate treatment is not used. Failure to give proper treatment may result not only in abortion but also in the death of the mother in some instances, especially with malignant tertian infections. Children born of malarious mothers are often premature and suffer from marasmus, which often results in early death. Treatment should never be withheld in pregnant cases, and mepacrine is considered by some to be the drug of choice. All malarial attacks in pregnant women should be treated as for threatened abortion or miscarriage.

In malarious areas, any post-partum rises of temperature should be suspected to be malarial, and the blood should always be examined. Appropriate therapy must be started at once.

(4) THE DIAGNOSIS OF MALARIA.

In the absence of blood examination malarial fever may be very difficult to diagnose, *as it may simulate or be simulated by any other disease known to medical science.* Although the classical symptoms of the disease have been summarised above, many cases, especially primary attacks of malignant tertian malaria and infections in children, are markedly atypical. Many deaths have occurred because of the failure to recognise and treat as malaria, cases showing atypical manifestations.

In countries where this disease occurs, and particularly during the epidemic season, *all* febrile ailments should *always* be suspected to be malarial until the diagnosis is otherwise disproved. When there is any doubt as to the cause of such fever, anti-malarial treatment should be started early, more especially if the manifestations are severe.

It is important to remember that *malaria may complicate or be complicated by any disease (medical or surgical) known to medical science.* The mere presence of some other obvious disease does not rule out the concomitant presence of malarial disease in persons who have been exposed to the infection, nor does the presence of malarial parasites in the blood negative the presence of some other disease which may be responsible for most of the clinical manifestations observed.

The rigors of malaria have been thought to be due to cholangitis, liver abscess, ulcerative endocarditis, pneumonia, occult sepsis, etc. Some cases at their onset may resemble influenza, or some other mild ailment, and in consequence specific treatment has been delayed until it was too late to prevent serious damage.

In malarious countries one or more blood examinations should be made before any abdominal operation is performed, especially if fever is present. If this cannot be done at once, a slide should be taken for later examination. Too many abdominal operations have been performed for con-

ditions which were purely malarial in origin and *not* surgical. If any reasonable doubt exists, always give anti-malarial therapy a trial, and, if the symptoms disappear, complete the course. In all patients who have been exposed to malaria, a rise of temperature after operation, injury or child-birth should be suspected initially to be malarial.

(i) **Fever.**—Malaria should always be suspected in any acute febrile paroxysm developing during or after residence in a malarious place, especially if it follows upon premonitory symptoms of the types mentioned above. The fever may not show the classical stages and periodicity. The latter may not be apparent in temperature charts made 12-hourly, but may be indicated in 4-hourly ones. Primary attacks often show quotidian fever of an intermittent or remittent type. Most malarial paroxysms, especially benign tertian ones, begin more commonly in the morning or early afternoon and the fever may fall towards evening, while in septic diseases it is more usual for the temperature to rise in the later afternoon and be high in the evening. In chronic infections low typhoid-like fever may occur.

(ii) **Parasites.**—The bloods of all persons developing fever after exposure to malarial infection should be examined, at least once daily if possible, for malarial parasites on several consecutive days, or until a diagnosis is made. Parasites are usually more easily found several hours after the height of a paroxysm than at its acme.

The finding of parasites is the only certain diagnosis of malarial infection, but failure to find them does *not* exclude that disease. Parasites may be absent from, or very scanty in, the peripheral blood in patients taking quinine or mepacrine, in certain cerebral cases, and in the early stages of a primary attack of malignant tertian malaria. In such cases the blood should be examined at least twice daily (preferably oftener and by the thick-film method).

The onset of *pernicious symptoms* should be anticipated, especially in malignant tertian infections, and appropriate steps taken if (a) more than 4 per cent. of the red blood cells are infected, (b) if half-grown or pigmented asexual forms of *P. falciparum* are found in the peripheral blood, (c) if more than 5 per cent. of the infected red cells have two or more parasites, (d) if very numerous asexual parasites persist in the peripheral blood, and the temperature remains high in spite of adequate oral administration of specific anti-malarial drugs, or (e) the parasite prevalence in the capillary blood is more than 10 per cent. higher than in the venous (count 1,000 red cells in each).

Even if facilities for blood examination are not available on the spot, blood smears should be made (a piece of window glass will do, if microscope slides be not available). These should be sent to the nearest laboratory for examination and report. They will help to confirm the diagnosis in case of doubt, and may reveal the cause of death, should the patient die. *Post-mortem* tissue smears are very useful in diagnosing the cause in suspected deaths from malaria. When it is impossible to make a complete post-mortem examination, smears may be obtained by splenic or bone-marrow puncture or from the brain. In the latter instance, a hole is bored through the supra-orbital plate by raising the

upper eye-lid and making a hole with a piercer, starting through the conjunctiva in the posterior fold of the upper fornix. A long stout exploring needle is run into the brain along the track thus made, and some brain material aspirated from which smears can be made for examination.

(iii) **Therapeutic Tests.**—If adequate doses of the drug of choice fail to reduce the temperature to normal in 5 (usually 3) days suspect either that the drug is not being taken, retained or absorbed, or that the *continued* pyrexia is due to some other disease.

(iv) **Blood.**—Untreated malaria may produce a very rapid anaemia of the secondary type. Fever, with a leucocytosis which lasts more than a few hours is not of purely malarial origin, but the occurrence of leucopaenia with a relative increase of the mononuclear cells and with fever is very suggestive. Chronic anaemia, especially if accompanied by some jaundice, splenomegaly and fever (often low), may be due to malaria. In such cases a course of malarial therapy may clear up the condition.

(v) **Splenic Enlargement.**—Probably occurs in all cases of acute malarial infection. In the early stages of an acute primary attack, the swelling is due to acute congestion and the organ is so soft that it is usually difficult to palpate. This is especially the case in adults with thick abdominal walls due to muscular or fatty development. Splenic enlargement is detected more frequently in chronic infections. The presence of such a spleen is, therefore, of value in diagnosis while its absence is much less so. Splenic pain and/or tenderness are not uncommon.

(vi) **Miscellaneous.**—A rise in urinary urobilin and urobilinuria occurs during the attack and for a few days afterwards. It is not, however, pathognomonic of malaria. Albuminuria is not very uncommon. In severe malaria the skin of the patient may rapidly develop a saffron-yellow tint of varying intensity. Herpes are not an uncommon sequel of benign tertian paroxysms.

Summary.

1. *Always* suspect malaria in *every* sick person in a malarious area, particularly if he has fever, even in the absence of any previous history of malarial attacks. *The absence of fever at the time of examination does not exclude malaria.*

2. *Always* get a blood examination made as soon as possible, and have this repeated, at least daily, until a diagnosis is reached.

3. The presence of obvious anaemia, jaundice and splenomegaly is suspicious.

4. Remember that malaria may simulate many other diseases, both medical and surgical, and in some cases withholding early treatment may have very serious consequences. If the patient is obviously ill and facilities for rapid blood examination are not available, start appropriate anti-malarial therapy *at once*. This is especially necessary if any indications of pernicious manifestations are observed.

(5) PROGNOSIS IN MALARIA.

Malaria is a very treacherous disease in which dangerous manifestations may develop without much warning, especially in children. Under epidemic conditions and where the type of infection is severe, it must always be regarded as a serious condition.

Deaths are more common at the two extremes of life, and in women than men. The debilitated and under-nourished resist malaria badly. The prognosis may be influenced very adversely by intercurrent affections.

The prognosis in severe cases depends almost entirely upon the establishment of very early diagnosis and prompt treatment. Failure to obtain these makes malaria a serious disease, and has resulted in a large number of deaths. With early adequate treatment the death rate from uncomplicated malaria is very low, especially among adults. The occurrence of pernicious symptoms is always of grave prognostic import, particularly if these be cerebral or algid, or if in children.

(6) GENERAL MANAGEMENT OF A CASE OF MALARIA.

A. During the Attack.

(i) The patient should be put to *bed*, and kept there, until the acute febrile attack is ended, and usually for at least 2 or 3 days longer. Severe attacks require longer rest, especially if primary and due to the malignant tertian parasite. Pernicious cases should not be allowed to leave bed or sit up for meals until at least a week after the temperature is normal and symptoms have disappeared. Transfer to another place should be avoided during this period. A very careful watch should always be kept for the premonitory indications of pernicious manifestations, especially the cerebral type, and for circulatory collapse.

(ii) Specific drug treatment in adequate dosage must be started immediately a diagnosis is made. *If in doubt*, it is wiser to treat a case of fever as malarial and start specific treatment at once, particularly if it is severe or the onset of pernicious symptoms is anticipated. Early purgation is recommended (*vide infra* "Intestinal Derangements") and alkalisation (*vide infra* "Alkalies").

(iii) (a) **During the Cold Stage of the Paroxysm.**—Blankets and hot bottles should be used, and copious drinks of hot fluid (tea, beef-tea, lemonade, broth, etc.) given to encourage sweating; a dose of some simple diaphoretic may be used.

(b) **During the Hot Stage.**—The patient should be sponged with tepid water and vinegar, and cold compresses may be applied to the head. The temperature must be taken frequently. If it rises to 104°F. or over, tepid sponging should be used to bring it down to 102°F. and repeated as often as the temperature again reaches the high level. (In such cases the temperature should be taken every 10 minutes, and if it goes up to 106°F., measures for heat-stroke treatment should be applied.) Care should be taken that the temperature is not brought below 102°F. by cold sponging, cold baths, ice-packs, etc., otherwise there is a danger of

collapse, especially if hyperpyrexia has been present. Copious alkaline drinks (lemon-squash, barley-water, soda, etc.) with plenty of sugar should be given. As a rule avoid anti-pyretics. For severe headache, aspirin or phenacetin can be taken, but the latter drug should always be combined with caffeine to counteract any tendency to heart failure.

(c) **During the Sweating Stage.**—The patient's clothing and bedclothes should be changed frequently. Watch for collapse, and if signs of blueness or feeble pulse are observed, stimulants should be given.

(iv) **Restless cases** should be nursed on the ground to avoid injury. Care should be taken that in restraining such cases the spleen is not ruptured. In very violent cases it may be necessary to give sedatives—morphia or barbiturates. Retention of the urine should be watched for in comatose cases.

(v) During the attack a light fluid diet should be given but the patient *must not* be starved. Citrated milk is useful during the febrile stage; fats should be avoided at all stages, and meat given but sparingly or not at all. Plenty of carbohydrates, especially sugar, help to protect the liver; while an abundance of green vegetables and fruit (oranges, tomatoes, apples, pineapples, etc.) are useful in increasing the alkali reserve. The patient should be made to take large quantities of sweetened alkaline drinks at all stages. If alcohol be given, it should be in moderation, preferably not spirits.

(vi) Patients who have lost much fluid by perspiration, vomiting and diarrhoea, should be given salt to replace that lost. In choleraic cases, it may be necessary to give intravenous injections of physiological (or even hypertonic) saline solutions, or of glucose-saline solutions by intermittent or by continuous drip methods.

B. During Convalescence.

During the convalescence, a nutritious diet should be insisted on. This should contain good biological proteins, adequate vitamins especially B. and iron. (Red meat, bread reinforced with wheat germ or rice polishings, fresh and dried fruit, such as peaches and apricots, are of special value.) Any secondary anaemia is treated with iron, arsenic and liver therapy, if severe (*vide infra*).

(7) THE SPECIFIC TREATMENT OF AN ACUTE ATTACK OF MALARIA.

This should be started immediately a diagnosis of malaria has been made, because attacks of malignant tertian malaria may develop serious pernicious symptoms with little warning and the life of the patient may depend upon early and vigorous treatment.

I. Anti-Malarial Drugs.

The drugs of value in controlling and curing the acute clinical attacks of malaria are quinine, "Paludrine" and mepacrine. The effects of these drugs in diminishing the relapse rate and in hindering the spread of

infection, are sometimes reinforced by the administration of pamaquin. The latter drug has, however, little or no value in curing *acute* clinical attacks of the disease.

The parasitocidal actions of these anti-malarial drugs are indicated in the following table :—

TABLE
Action of Drugs on Different Stages of the Malarial Parasites.

Drug.	Asexual Parasites.			Sexual Parasites.		
	B.T.	Qt.	M.T.	B.T.	Qt.	M.T.
Quinine ..	+++	+++	+++	+++	++	o
*“Paludrine” ..	+++	++	+++	+++	N.K.	+++
Mepacrine ..	+++	+++	+++	+++	++	o
Pamaquin ..	++	++	o	+++	+++	+++

NOTE.—B.T. means benign tertian parasites ; Qt. quartan parasites, and M.T. malignant tertian parasites ; + + + indicates a very marked destructive action ; + + a less marked action and o an absence of destructive action. N.K. means “not known.”

From this table it is seen that the action of quinine and mepacrine on the parasites are identical, although some variation in the degree and rapidity of their effects on clinical symptoms has been recorded with different species and strains of parasites.† The available evidence goes to show, however, that for the routine treatment of ordinary acute malarial attacks the two drugs are almost equally effective.

Apart from its use during the first few days of an acute attack, quinine is much less often used now-a-days for routine treatment if mepacrine be available. It has, however, a special place in the treatment of the following conditions :—

- (a) Cerebral or other pernicious attacks of malaria requiring intravenous injection.
- (b) Malaria in infants and very young children.
- (c) Occasionally for cases of malaria whose symptoms do not react quickly enough to mepacrine medication.
- (d) Malaria in patients showing severe mepacrine intolerance.
- (e) Patients for whom mepacrine is not available.
- (f) Patients showing repeated relapses in spite of proper mepacrine treatment.

* The action of “Paludrine” is probably not on the gametocytes in the blood but it inhibits the development of the sexual cycle at a later stage in the stomach of the mosquito.

† In the malarial infections of some regions, quinine has been reported to have a more rapid action in clinical cure than has mepacrine in the usual dosage. Apart from any question of specific action on special strains of parasite, this is probably due to the more rapid manner in which the blood concentration of quinine rises. In recent work, by the giving of larger doses of mepacrine (0.6—1.0 gm. on the first day of treatment), this discrepancy has been reduced.

The *oral administration* of anti-malarial drugs should always be used for general routine treatment. It is the method of choice in the vast majority of cases.

Parenteral injections should *never* be given as a routine, but only in special circumstances (*vide infra*).

A. The Oral Administration of Anti-Malarial Drugs.

The four anti-malarial drugs used by the oral route are quinine, "Paludrine," mepacrine and pamaquin. The absorption of these drugs should be assisted by opening the bowels freely very early in the attack and keeping them open (*vide infra*).

The administration of sugar and alkalies is very useful, not only in helping to diminish any unpleasant effects of the drugs, (*vide Appendix 2*), but possibly also in helping their therapeutic action, especially when large daily doses are being given.

(i) **Quinine.**—The salts of this drug should always be administered in solution whenever possible. Those usually given in this manner are the sulphate and the hydrochloride. A good prescription for quinine solution is :—

Quinine Sulphate or Hydrochloride	10 grains
Citric Acid*	30 ..
Magnesium Sulphate or Sodium Sulphate	20-60 ..
Syrup	to 1 ounce

It may occasionally be necessary to give quinine in the pill or tablet form, but solutions are always preferable, because the former sometimes passes through the intestines without being disintegrated and absorbed. This is especially the case with sugar-coated pills (which should never be used) and those of the less soluble salts of the drug. Pills and tablets should be made of the more soluble salts, such as the dihydrochloride, the bisulphate or the hydrochloride,† preferably the first. The solubility of such preparations should always be tested periodically, and if these do not disintegrate and dissolve readily in water, they should be well crushed, or better still put into solution before use. The administration of tablets or pills should always be followed by copious draughts of water, preferably acidulated (lemon squash). As explained below, their efficacy is probably increased by the simultaneous administration of a small dose of a saline aperient.

The dosage of quinine for an adult is 10 grains thrice daily.‡

* Dilute sulphuric or hydrochloric acids, minims 10, may be used if citric acid is not available, but the latter is much preferable. Acid is not needed to dissolve the very soluble salts (e.g., bisulphate and dihydrochloride).

† The quinine alkaloidal content 10 grains of the bisulphate is only equal to about 8 grains of the sulphate of the dihydrochloride and about 7 grains of the hydrochloride. For practical purposes 12½ grains of the bisulphate are taken as equivalent to 10 grains of the other salts.

‡ Children stand quinine well. The dosage should be 0-7 years—quarter of a tablet ; 8-14 years—half of a tablet ; 14 years and over—adult dosage. If euquinine or totaquina be used, the dosage should be at least one and a half times that of ordinary quinine salts.

(ii) **Paludrine**.—More experience with “Paludrine” in the treatment of overt attacks of malaria is necessary before its optimum dosage as a schizonticidal drug for all strains of malaria parasite is finally determined. The immediate clinical response to treatment sometimes appears slower than with mepacrine or quinine, but the ultimate results of paludrine therapy compare very favourably with either of these drugs except possibly in Africa; here a Lagos strain of *P. falciparum* has recently proved resistant to the schizonticidal action of “Paludrine” though not to its causal prophylactic action, i.e., on the pre-erythrocytic forms (Covell & Shute).

Though gametocytes persist apparently unharmed in the blood of malaria carriers who are taking paludrine, the drug inhibits the subsequent development of the sexual cycle in the stomach of the mosquito, so that oocysts fail to develop and sporozoites never appear in the salivary glands of anophelines feeding on such blood.

The therapeutic course of “Paludrine” consists of 1 to 2 tablets (each = 0.1 gramme) thrice daily after food for 10 days.

In hyper-infection or in patients showing pernicious symptoms such as hyperpyrexia, cerebral symptoms, cardiovascular collapse, or severe gastro-intestinal manifestations, this treatment should be combined with intramuscular injections of mepacrine hydrochloride (0.3 gramme) or intravenous injections of quinine dihydrochloride (grains 10). These injections should be given without delay and repeated as required.

Recent experimental research has shown that the combined treatment of quinine and “Paludrine” not only has the effect of rapidly relieving the fever but has the ultimate effect of curing the attack completely and avoiding relapses which are liable to recur if quinine is given alone.

Consequently for the treatment of an acute attack give 2 tablets of quinine bisulphate or quinine dihydrochloride (5 grain tablets) twice daily for 3 days and in addition give 2 tablets of “Paludrine” (0.1 gramme tablets) 3 times daily for 10 days making a total of 12 tablets of quinine and 60 tablets of “Paludrine.” Wash down the tablets on each occasion with a glass of water.

This treatment, if available, should be given in preference to mepacrine and in a case of actual malaria should cause a fall in temperature and relief of symptoms within 36 hours. Nevertheless the full course of treatment must be given.

(iii) **Mepacrine Hydrochloride** (Atebrin; Atabrine; Quinacrine; Chinacrine; Acriquine; Italchina). For routine treatment this is the drug of choice. It is issued in the form of yellow tablets, each usually containing 0.1 gramme of the drug.

It should not be given on an empty stomach. Copious draughts of non-alcoholic fluid should be given before and after administration. Such fluids as sweetened tea, or fruit juice, etc., are particularly suitable.

The routine dosage for an adult is 3 tablets (0.1 gramme) of mepacrine immediately, repeat this in four hours and once again after 12 hours, making a total of 9 tablets in the first 24 hours. On the next day give 2

(0.1 gramme) tablets three times at intervals of 8 hours, making a total of 6 tablets in the second 24 hours. For the next 4 days, 1 tablet (0.1 gramme) is given thrice daily. This completes the full course of a total of 27 tablets.*

(iv) **Pamaquin** (plasmoquine ; praequine), is another synthetic drug, given orally in tablet form. *It must never be given parenterally.* It has no practical value in the cure of acute clinical attacks. It is useful, however, in reducing the relapse rate, especially in benign tertian infections, and in preventing the spread of infection to mosquitoes by reason of its devitalising effects on gametocytes, especially those of *P. falciparum*.

The total daily adult dosage for repeated use should not exceed 0.03 gramme given in divided doses, as it is liable to cause toxic symptoms in higher dosage (*vide* Appendix 2). It may be given at the same time as quinine or "Paludrine," *but must never be given concurrently with mepacrine.* Pamaquin should never be given except under medical supervision, preferably in hospital. It should not be issued to out-patients for the routine treatment.

B. Parenteral Injections of Anti-malarial Drugs.

The oral administration of antimalarial drugs is always the method of choice. Parenteral injection should only be used in special circumstances (*vide infra*), and *never* for routine treatment. As a rule all comatose patients in malarious areas, especially during the epidemic season, should be considered to be malarial and given parenteral treatment. It is better to give unneeded therapy than to risk death from failure to give specific treatment. The drugs used for parenteral injection are quinine and mepacrine ; *pamaquin must never be given by this route.* Parenteral methods are employed when very rapid drug action is urgently needed, which cannot be obtained sufficiently rapidly by the oral route, or when for some other reason the latter method of administration is impossible. As soon as the indications for parenteral injection have passed off, and urgent causes for its use controlled, this method of medication should always be replaced by the oral one at the earliest moment. The drug treatment then proceeds as in an uncomplicated case.

Such injections may be given either by the intravenous or the intramuscular route, *never* subcutaneously. Quinine may be used by either of the former routes, but mepacrine and "Paludrine" should only be given intramuscularly, *never* intravenously.

(a) Intravenous Injections of Quinine

The technique for this procedure is detailed in full in Appendix No. 1. The following are the chief indications for its use :—(1) any signs of involvement of the central nervous system ; (2) more than 4 per cent. of the red cells attacked by malarial parasites ; (3) more than 5 per cent. of the parasitized red cells showing two or more parasites ; (4) the

* Young and undernourished children usually do not stand mepacrine as well as they do quinine. If tablets are not easily administered, they may be crushed in sweetened milk or fruit juice. The dosage for children should be 0.7 years—quarter of a tablet ; 8–14 years—half of a tablet ; 14 years and over—adult dosage.

occurrence of pigmented asexual forms of *P. falciparum* in the peripheral blood ; (5) hyperpyrexia ; (6) algid or collapsed conditions ; (7) severe bilious or untractable vomiting, or other cause preventing the retention or absorption of the drug by the oral route ; (8) paroxysm after paroxysm not cut short by adequate oral treatment.

Intravenous injections of quinine, especially if given too quickly and in concentrated solutions, may sometimes cause a rapid fall in blood pressure with collapse. Special care should be taken in patients with organic disease of the heart, marked anaemia and debility, and severe jaundice. Injections are better given when the stomach is not full. Errors in technique may also give rise to local necrosis and thrombosis in the vein. When proper precautions are taken, these risks are relatively slight, and are greatly out-weighed by the life-saving effects of such injections.

The dosage is $7\frac{1}{2}$ –10 grains of quinine dihydrochloride or dihydrobromide at one injection. When possible this should be given as a transfusion in a large amount of fluid (200–300 cc.), but, if facilities for *immediate* transfusion be not available, the initial dose may be given in 10–20 ccs. fluid (vide Appendix No. 1). This dosage may be repeated in 6–8 hours, if the patient's condition demands it, and adequate oral administration cannot be started. Usually a single injection is sufficient to enable oral administration to begin. Not more than 30 grains of quinine should be given parenterally in 24 hours, but the patient should, however, receive and retain at least a total of 30 grains daily, irrespective of the routes used.

(b) Intramuscular Injections of Mepacrine or Quinine.

Intramuscular medication has no special virtue over oral treatment, when the latter can be employed and the drug is absorbed. Indeed in the case of quinine the rate of absorption after oral administration is more rapid.

Such injections always cause a greater or less degree of necrosis at the site of the injection. Apart from damage to muscles resulting in septic or aseptic abscesses, if any important nerves or vessels are involved very serious results may follow. Quinine is believed to be much more destructive than is mepacrine by this route, so that the latter should be used when this method becomes necessary.

Such injections cannot replace intravenous medication with quinine in urgent emergencies. They may, however, be used to reinforce or supplement the latter and maintain their action, or be substituted for them when for technical or other reasons it is not possible, or desirable, to use intravenous quinine medication.

The chief indications for the use of intramuscular injections are :—
(i) where it is not possible for technical reasons to find a suitable vein for intravenous injection, when that method is indicated (*vide supra*) ;
(ii) sometimes in very collapsed patients with circulatory weakness when facilities for intravenous injection of quinine diluted with large amounts

of physiological saline or sugar solutions, are not quickly available ; and (iii) mepacrine may sometimes be given by this route to reinforce the action of anti-malarial drugs given by other methods.

Full details of the technique of intramuscular injection are given in Appendix No. 1.

(1) Intramuscular Injections of Mepacrine.

This is the only parenteral route by which mepacrine should be given. By this route it is preferable to quinine because of its less necrotic action and its quicker absorption. Two salts of mepacrine have been used for such injections—(i) mepacrine methanesulphonate ("Atebrin for injection" ; Atebrin musonate), and (ii) mepacrine dihydrochloride (Atebrin dihydrochloride). These are issued in ampoules or sterules, either as powders or in sterile solutions. The powder is highly soluble in water.

Serious toxic effects have been reported after such injections in children.

(i) **Mepacrine Methanesulphonate** is issued in ampoules containing 0.125 and 0.375 gramme, equivalent to 0.1 and 0.3 gramme respectively of mepacrine hydrochloride. These amounts are dissolved in 3 ccs. and 9 ccs. respectively of distilled water. The daily dosage is 0.375 gramme, one-half injected into each buttock.

(ii) **Mepacrine Dihydrochloride.** Doses of 0.3 gramme dissolved in 10 ccs. distilled water or physiological saline and injected intra-muscularly into the buttock.

These doses of mepacrine may be repeated, if necessary once but rarely twice, after an interval of 6–8 hours. Such injections should not be given on more than two successive days. Oral administration should replace parenteral as soon as possible. The total amount of mepacrine given by both routes should not exceed 1.5 grammes in 48 hours.*

(2) Intramuscular Injections of Quinine

The very soluble salts of quinine should be used for this purpose—quinine dihydrochloride and the dihydrobromide. These injections should be avoided, if possible, as painful nodules may be left, and severe abscesses and even tetanus are sometimes reported after their use. They should *never* be used as an alternative to oral treatment. The usual dosage by this route is $7\frac{1}{2}$ –10 grains of quinine dissolved in 4–10 ccs. normal saline solution. Half the dose is injected in each buttock to reduce the necrotic effect. Not more than 2 or at the outside 3 injections should be given in 24 hours. If more than one injection is needed it is usually an indication that either the intravenous route should be used for the drug, or mepacrine should be substituted. The technique of injection is detailed in Appendix No. 1.

* There appears to be no contra-indication to the use of quinine and mepacrine at the same time, as there is in the case of pamaquin and mepacrine.

II. Adjuvant Measures to assist the Efficacy of Drug Treatment.

As in all therapeutic methods, steps should be taken to ensure that the drug prescribed is taken, retained and absorbed under conditions favourable for its maximum therapeutic action. When anti-malarial drugs are liable to cause undesirable manifestations, precautionary measures should also be carried out to diminish the likelihood of such occurrences (*vide* Appendix No. 2. "The Toxicity of Mepacrine and of Pamaquin").

(a) **Vomiting** may be of frequent occurrence, especially in severe attacks of malaria, and it may prevent the retention of the drug in therapeutic doses. Frequent small doses of an alkaline mixture will help greatly to diminish vomiting. (The alkaline mixture mentioned below may be given, or sod. bicarb. or sod. citras 60 grains in 2 ounces of water.) If the patient vomits, the mixture should be repeated. It may usefully be preceded by an oral dose of 20 minims of adrenalin solution (1/1000) repeated if necessary.* Ice may be given to suck, and hot fomentations or a mustard leaf to the epigastrium may be useful. Such measures usually stop vomiting. In very severe cases 5 minims of tinct. opii may be given and repeated at half-hourly intervals up to a maximum of four doses. The specific drug is administered in the intervals between attacks of vomiting until a therapeutic dose is retained. Solid food should be avoided just before the time of an expected paroxysm.

(b) **Intestinal derangements** are common in malaria and often interfere with the absorption of anti-malarial drugs. The bowels should always be opened well very early in the attack. The best measures are an immediate dose of calomel (about 3 grains) followed by a saline *aperient* (magnesium or sodium sulphate 1 ounce). At the same time the lower bowel should be cleared by an enema. To ensure continued absorption it is wise to give a saline *aperient* daily, or to include it in the solution of the specific drug (*vide supra*, "quinine mixture"). Such mild purgation also helps to reduce the chances of toxicity from mepacrine or pamaquin.

(c) The administration of *alkalies* in large doses helps absorption and probably enhances the specific action of anti-malarial drugs. By their action on the kidneys and alkali reserve, they also diminish the tendency to toxicity with mepacrine and with pamaquin, and are probably helpful in preventing or ameliorating the manifestations of blackwater fever.

Repeated doses of alkali (sod. bicarb. or sod. citras) should be given at the commencement of a malarial attack to make the urine alkaline quickly, and the drug should be repeated sufficiently frequently to keep it so.

The following is a convenient form of alkaline mixture :—

Sodium Bicarbonate	60 grains
Sodium Citrate ..	40 "
Calcium Carbonate or Calcium Chloride ..	3 "
Water ..	to 1 ounce

(As this mixture is not a complete solution, it should be well shaken before being taken.)

* If adrenalin be not available, some workers advise the administration of doses of 3 drops of a 5 per cent. aqueous solution of carbolic acid.

(d) **Sugar** in large amounts up to 4 ounces or more daily is useful in malarial cases. Apart from its nutritive value, it acts as a cardiac tonic (especially in algid cases), and also helps to protect the liver upon which not only a considerable amount of the pathological effects of the malarial infection falls, but also any toxic actions of the synthetic drugs, mepacrine and pamaquin. Glucose given intravenously may also help to increase the osmotic pressure of the blood and so help capillary flow, as well as combatting vomiting due to acidosis (*vide supra*).

(e) A copious *fluid* intake must be ensured to replace the large amounts lost by perspiration, vomiting, etc. This is especially necessary during the hot weather and for this purpose a daily intake of 5-7 pints (3-4 litres) is needed. If sufficient cannot, or will not, be taken orally, intravenous injection of saline solution is necessary. An attempt should be made to keep the urinary specific gravity at 1010 or less. Care must, however, be taken not to overload the circulation.

(f) Special measures may also be necessary to replace the large amounts of *sodium chloride* lost in the excessive perspiration, which loss predisposes to heat exhaustion. A liberal oral salt intake must be ensured and this may be supplemented by the intravenous route, while in choleraic cases hypertonic solutions may be beneficial. Such injections or transfusions can with advantage be combined with glucose (5 per cent.). Doses as large as 200-400 ccs. may be given if the circulation is not embarrassed thereby, and, if larger amounts are needed, these may be given by the drip-transfusion method at about 50 drops to the minute.

(g) the post-malarial *anaemia* may require treatment. *Arsenical* drugs, such as stovarsol and novoarsenobillon, are very beneficial in the anaemia and debility of convalescence. On account of the heavy burden which malaria throws on the liver, such medication should always be combined with the administration of sugar and alkali at the same time. *Iron* tonics should also be used and their actions are usually reinforced by liver and vitamin therapy with appropriate diet (*vide supra*).

(h) In cerebral cases with violent delirium or extreme restlessness, *sedatives* may be necessary. The barbiturates or morphia are very useful. Intravenous or even chloroform anaesthesia may be needed in very violent or convulsive cases, not only to control them but also to enable parenteral injections to be given.

III. Summary of Routine Drug Treatment of Malarial Attacks.

The specific drug treatment of malaria should be started immediately the diagnosis is made. The action of the drugs should be assisted as far as possible by the adjuvant measures described above (purgation, alkalies, sugar, etc.).

(A) Treatment of a Simple Attack of Malaria. Any of the following treatments may be used depending on the drugs available and other considerations :—

(i) Quinine grains 10 thrice daily (preferably in solution) for ten days.

(ii) Mepacrine, each tablet of which contains 0.1 gramme ($1\frac{1}{2}$ grains). On the first day 9 tablets are given in divided doses, on the second 2 tablets are given thrice daily and from the third to the seventh day one tablet thrice daily after food (Total = 3.0 grammes).

(iii) "Paludrine" one to two tablets (each = 0.1 gramme) are given thrice daily after food for ten days.

(iv) "Paludrine" and Quinine.

Recent experimental research has shown that the combined treatment of "Paludrine" and quinine not only has the effect of rapidly relieving the fever but has the ultimate effect of curing the attack completely and avoiding relapses which are liable to recur if quinine is given alone.

Consequently for the treatment of an acute attack give 2 tablets of quinine bisulphate or quinine dihydrochloride (5 grain tablets) twice daily for 3 days and in addition give 2 tablets of "Paludrine" (0.1 gramme tablets) 3 times daily for 10 days making a total of 12 tablets of quinine and 60 tablets of "Paludrine." Wash down the tablets on each occasion with a glass of water.

This treatment should be given in preference to mepacrine and in the case of first attacks should cause a fall in temperature and relief of symptoms in 36 hours. Nevertheless the full course of treatment must be given.

In the case of chronic malaria with exacerbations it will be for the ship's surgeon to decide whether the use of quinine combined with "Paludrine" is desirable in the light of the possibility that it may promote an attack of blackwater fever.

Chronic cases of malaria as relapses are, of course, much more likely to be found among passengers who have resided for some time in a malarious country than among members of ships' crews.

Some authorities prefer mepacrine to quinine as they consider there is less likelihood of precipitating blackwater fever in chronic infections with *P. falciparum*. It is also possible that mepacrine is to be preferred to "Paludrine" in certain African cases, for Covell & Shute have recently studied a Lagos strain of *P. falciparum* which proved resistant to the schizonticidal action of "Paludrine" even in maximum dosage.

(B) Treatment of Attacks of Malaria showing Pernicious or Abnormal Symptoms.

In the special circumstances detailed earlier, quinine or mepacrine are given by parenteral injection. Intravenous injections of $7\frac{1}{2}$ –10 grains of quinine repeated in 6–8 hours is the method of choice. When this method is not practicable or requires reinforcement, intramuscular injections of quinine or mepacrine (preferably the latter) may be used. The adjuvant and subsidiary methods of treatment for special syndromes mentioned below should be employed also.

The following are some subsidiary methods in the treatment of special malarial syndromes :—

- (i) **Hyperpyrexia.** This should be treated as for heat-stroke (ice-bags to the head ; tepid or cold sponging or baths ; ice packs, etc., to reduce the temperature).* Collapse should be watched for, and if necessary cardiac stimulants (adrenalin, pituitrin, digitalin, camphor, etc.) given.
- (ii) **Cerebral Symptoms.** Ice-bags should be applied to the head. An injection of 15 minims of adrenalin solution (1/1000) may be useful. If coma continues or meningeal symptoms are present, lumbar puncture with the withdrawal of about 20 ccs. fluid may be tried, especially if there is excess pressure. If the patient is rowdy give sedatives.
- (iii) **Algid or Collapse Symptoms.** These should be treated as for acute shock. Quinine may be given intravenously in a pint of 5 per cent. glucose-saline solution, care being taken not to embarrass the right side of the heart. The recurrence of collapse may be prevented by using continuous drip glucose-saline afterwards. Adrenalin and cardiac stimulants are usually needed.
- (iv) **Gastro-intestinal Symptoms.** Injections of adrenalin are useful. The choleraic form should be treated for loss of fluid as in cholera. An injection of morphia often helps in dysenteric cases, and also in persistent hiccough.

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* See note on general management of the hot stage.

APPENDIX No. 1

TECHNIQUE OF PARENTERAL ADMINISTRATION OF ANTI-MALARIAL DRUGS

The very strictest aseptic precautions must be taken in all parenteral injections. This is more especially the case with intramuscular ones, which always cause varying degrees of muscular necrosis. This may be considerable with quinine but less with mepacrine.*

Drug Preparations for Parenteral Injection.—Special preparations (ampoules, sterules, etc.) are manufactured for this purpose and have been described in the text. They should be used if available.

Apparatus for Injection. (i) For the parenteral injection of small amounts of fluid, the syringe should be an all-glass one, if possible. The needle (preferably platino-iridium) should be very sharp and if possible new. The apparatus should be sterilised, preferably in a steam or a hot-air steriliser, otherwise boiled in a 5 per-cent. carbolic acid solution for 10 minutes and then rinsed in sterile water or saline. (ii) For injections of large amounts of fluid the ordinary methods of transfusion should be used.

A. Parenteral Injections of Quinine

Wherever possible specially prepared sterile preparations should be used. If such solutions show any precipitate they should be heated and, if the opacity does not clear up, they must be discarded.

In addition to these sterile solutions special tablets are sometimes issued for injections,† or it may be necessary to make up solutions from the powder. The quinine salts of preference are the dihydrochloride and the dihydrobromide. The bisulphate may be used in an emergency but is liable to decomposition on heating.

In making up solutions, 10 grains of quinine dihydrochloride should be dissolved in distilled water or physiological saline. If the solution be cloudy, it is filtered until clear. The clear solution is well boiled for at least 5 minutes, or, better, autoclaved for 15–20 minutes at 110–115°C.

1. Intravenous Injections of Quinine‡

The patient should always be kept strictly recumbent during and for several hours after the injection.

(a) Injections of Small Amounts of Concentrated Quinine Solution.

For this purpose a large syringe is used. The needle should be the finest possible so that the injection can be given very slowly, because quinine may cause circulatory collapse if introduced quickly into a vein. The dosage of the drug is dissolved in 10 or, better, 20 ccs. of fluid. The strength should not be greater than 1 grain to 1 cc.

* This necrosis, apart from the occasional occurrence of residual painful nodules, forms a very suitable nidus for bacterial growth. Abscess and even tetanus have been known to follow such injections of quinine.

† Tablets manufactured for oral administration should not be used, as they contain other ingredients which it may be inadvisable to inject parenterally.

‡ *Mepacrine must never be given intravenously.*

The technique of intravenous injection is described below :—

(i) Select a suitable large vein (usually the median basilic)* ; make this stand out prominently either by manual constriction of the arm or by a bandage. Paint the field of operation with iodine, and rub this off with alcohol so as not to obscure the vein. Get an assistant to hold the patient's hand firmly so that the needle does not become displaced during injection. See that the needle is firmly fixed on the syringe and that the syringe is working properly. In all cases the needle should be filled with saline before attempts are made at insertion, and its outer surface should be dried with sterile cotton wool.†

(ii) Pierce the vein in the direction of the shoulder and insert the needle until half its length lies inside the vein. Immediately release the pressure above the point of injection. Very gently withdraw a little blood into the syringe to make certain the needle is in the lumen ; if it is not, reapply the pressure, withdraw the needle slightly and again attempt to aspirate blood. *Never attempt to inject quinine unless absolutely certain that the point of the needle is free in the lumen of the vein*, because quinine solution in the tissues will cause necrosis.

(iii) When the needle is properly inserted, commence very slowly to inject the solution. If the needle is correctly placed there should be *no swelling at the point of injection and the patient should feel no pain there*. If swelling occurs, attempt to suck back as much of the fluid as possible from the puncture. In such conditions, if much solution has escaped into the tissues it is better to try another vein.

The solution should be injected *very slowly*, at least 20–30 seconds, being taken for each cubic centimetre, the longer the better. It is well to rest for 10–20 seconds after each cubic centimetre. During the operation watch the pulse carefully and if any signs of circulatory weakness are observed inject adrenalin or pituitrin, which should be ready beforehand.

(iv) When the injection is finished, aspirate a little blood into the syringe, withdraw the needle, paint the spot with iodine and cover with collodion.

The important points are—(i) strict sterility, (ii) avoidance of escape of the solution into the subcutaneous tissues, (iii) slowness of injection, and (iv) careful observation of the pulse.

Intravenous injections may be repeated in 4–6 hours, but very rarely thrice in 24 hours.

(b) Injection of large amounts of Dilute Quinine Solution.

Whenever possible and when the circulatory condition does not contra-indicate the injection of large amounts of fluid, quinine should be given in a very dilute solution. This is especially the case in algid and choleraic

* In children and in patients (especially collapsed or algid cases), with whom it may be difficult to insert a needle directly into a vein, it may be necessary to cut down. For this purpose the large vein in front of the ankle may be used.

† This is to diminish the chances of local necrotic action due to a deposit of the drug along the track of the needle.

patients. In urgent cases, however, do not wait while large amounts of saline are prepared ; give an injection of the concentrated solution and follow this up with a dilute transfusion if needed.

The dose of quinine is diluted with 200–400 ccs. of physiological saline solution, or with a 5 per-cent. solution of glucose saline. As with syringe injection the rate of transfusion should be slow, and not more than the equivalent of 1 grain of quinine should be given every 2 minutes.

2. Intramuscular Injections of Quinine or of Mepacrine.*

On account of the damage to tissue caused by such injections, more especially by quinine, the very strictest aseptic precautions must be taken. Intramuscular injections of quinine should only be given if appropriate mepacrine preparations are not available, or sometimes in children.

(a) Intramuscular Injections of Quinine.

The usual injection is $7\frac{1}{2}$ –10 grains of quinine dihydrochloride dissolved in 3–4 ccs. of physiological saline. It is better, however, to dissolve this amount in 8–10 ccs. and inject half on either side, thus diminishing the necrotic effect. The needle should be filled with saline and wiped dry with sterile cotton-wool before insertion.

A stout new needle or a platino-iridium one, at least $2\frac{1}{2}$ inches long, is used for injection. The usual site of injection is *deep* into the upper and outer quadrant of the gluteus maximus muscle in a line horizontal to the apex of the great trochanter or about 3 inches below the middle of the crest of the ilium. Great care must be taken to avoid the great sciatic nerve. After very careful sterilisation of the skin, the needle is introduced perpendicularly until it reaches the bone, it is then retracted for about $\frac{1}{2}$ inch.† Withdraw the plunger of the syringe slightly to be sure that the point of the needle is not in a vein. Inject the solution, distributing it as much as possible. After withdrawal of the needle, massage the spot thoroughly for two minutes at least, to help the diffusion of the solution. Paint the puncture with iodine and seal with collodion. Do not reinject on the same spot, use the other side. Other much less suitable sites used for intramuscular injections are : (a) below and external to the angle of the scapula, (b) the vastus externus muscle about the middle third of the outer side of the thigh, and (c) the deltoid muscle about 2 inches below the acromion process, avoiding the musculo-spiral nerve. Injections should always be intramuscular not subcutaneous and be placed deeply.

As much as 10 grains twice daily may be given, if required.

(b) Intramuscular Injections of Mepacrine.

The sterile methane-sulphonate or the dihydrochloride salt is dissolved in distilled water. The adult dosage is 0.375 gramme of methanosulphate or 0.3 gramme of the dihydrochloride salt given at a single injection into the buttock as in intra-muscular quinine injections.

* The indications for intramuscular injection have been given in Section 7, Para. B (b), page 20.

† The injection should never be made against a bone.

Toxicity of Mepacrine and of Pamaquin

(i) **Mepacrine.** This drug has a low toxicity but a very few persons have an individual idiosyncrasy which makes them liable to unpleasant by-effects, and much more rarely, to serious undesirable manifestations. Such symptoms are commoner in Europeans and in meat-eaters. They may develop either during treatment or after its cessation. Yellow discoloration of the skin is common, especially if administration is prolonged. It may begin after about three days and sometimes lasts weeks. It is not a toxic symptom, but due to the dye element of the drug.

While some mild disagreeable effects, mainly gastro-intestinal, may occur when suppressive treatment is started, these pass off quickly if the drug is continued, leading to habituation. Wide experience in the last few years has shown that true toxic effects with ordinary doses used are rare.

Some such unpleasant by-effects are headache, transient abdominal pains, diarrhoea, mental depression, giddiness, anorexia, and vomiting. Irritation of the skin may occur, and, after prolonged administration (prophylaxis), irritable thickening of the palms and soles has been reported.

Toxic symptoms are severe persistent headache, severe abdominal pains, and "cerebral excitement". The cerebral symptoms may resemble alcoholism and vary from restlessness and excitement up to serious confusional and maniacal psychoses, which usually clear up in a few days, when the drug is stopped. This effect may develop either during the administration of the drug, or even some days *after* this has ceased. Such psychotic manifestations are almost entirely confined to persons with previous histories of some mental instability, or when large doses are given. *Treatment* of toxicity consists in stopping the drug, giving purgatives, large doses of alkali and much sugar. When possible always give mepacrine after a meal, or at least with copious draughts of non-alcoholic fluids.

Epileptiform fits have been recorded after injections of mepacrine methanesulphonate in children. This method should not be used with them.

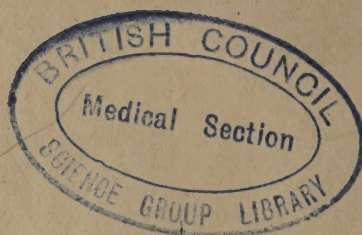
After mepacrine has been taken in a dosage of 0.1 gramme daily for several months, a lichen-planus-like condition occasionally develops. This is a serious complication and is a definite contra-indication to further use of the drug. It fortunately is rare, being encountered in only 0.1–0.2 per cent. of people taking mepacrine for suppressive purposes.

(ii) **Pamaquin.** In doses up to 0.03 gramme daily for short periods the toxicity of this drug appears to depend largely on individual idiosyncrasy. Slight cyanosis and milder degrees of abdominal discomfort, pain and vomiting are not uncommon, but where a larger and more prolonged dosage of pamaquin is being administered progressive increase

in the severity of these symptoms or the appearance of even slight jaundice or haemoglobinuria are indications for the immediate cessation of treatment with the drug for a serious or fatal toxæmia may suddenly supervene. This is shown as drowsiness, depression (mental and physical) intense cyanosis, severe abdominal pains, cholera-like vomiting and diarrhoea in some cases, methaemoglobinuria with albumen and casts, going on to coma and signs of liver necrosis.

To reduce the liability to toxicity, the dose for robust adult males should not exceed 0.03 gramme daily; this should be given in divided doses about $1\frac{1}{2}$ hours after meals.

Toxicity is treated by the use of purgation, alkalies, sugar and stimulants. Methaemoglobinuria is treated as for blackwater fever.



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